Unique Coordination Mode of Potassium Ions to Glycyrrhizin: X-ray Crystal Structure of Glycyrrhizin Dipotassium Salt

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The coordination of six potassium ions to glycyrrhizin (**1**) is shown in a crystal: two crystallographically independent (K1 and K2) and four symmetry-translated potassium ions coordinate to the oxygen atoms of the sugar-linkage moiety, and the K1 and K2 ions form seven and six coordination bonds with the neighboring oxygen atoms, respectively. Although three carboxyl groups of **1** are in an anionic state, two of the glycosides participate in the coordination bonds with the potassium ions.

Among triterpene oligoglycosides, which are the principal ingredients of Glycyrrhizae Radix, glycyrrhizin (**1**) is the most important principle. The structure analysis of **1** has been receiving much attention because of the evaluation of its conformation,[1] sugar-linkage, and coordination mode with counter ion such as K^+, Na^+, and NH_4^+.[2] However, **1** has been still resisting efforts of crystallization. On the other hand, **1** forms a tripotassium salt, which yields monopotassium salt on recrystallization from hot acetic acid. For liberation of the remaining cation, a strong cation exchange resin or dilute sulfuric acid is needed.[3] Thus, it is interesting to reveal which carboxylic acid group participates in the strong salt formation. Recently, we succeeded for the first time in the crystallization of dipotassium glycyrrhizate (**2**) using **1** monopotassium salt[4] dissolved in an aqueous solution containing 10% dimethylformamide (DMF) by slow evaporation (Figure 1). Since the crystals are thin and fragile plates and become opaque quickly in air, the structural accuracy is a little inferior to that usually reported.[5]

The molecular conformation of **2** is shown in Figure 2, and some selected bonding and conformational data are listed in Table 1.

The bond lengths and angles of three carboxyl groups clearly show that these are all in an anionic state, suggesting no notable difference among them in the potency for salt formation. The molecular dimensions of aglycon and diglycoside moieties are essentially the same as those of glycyrrhezin[6] and α-sophorose,[7] respectively, and the molecular conformation of **2** is defined with four torsion angles of H3–C3–O1–C1′ (ϕ1), C3–O1–C1′–H1′ (ϕ2), H2′–C2′–O3–C1″ (ϕ3), and C2′–O3–C1″–H1″ (ϕ4). The eclipsed orientation for ϕ1 (−19.4°) and ϕ3 (24.8°) is due to an anomeric effect, and the gauche orientation for ϕ2 (38.7°) and ϕ4 (56.1°) is due to the exo anomeric effect of oligosaccharide.[8] Similar conformation has been observed in the crystal strucutre of **1** ammonium salt.[2]

A structural feature of **2** is the simultaneous coordination of

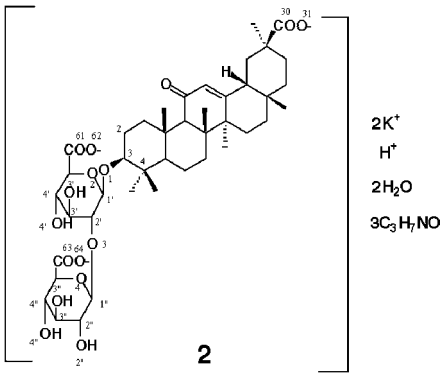

Figure 1. Molecular structure of **2** (dipotassium salt of **1**), together with some atomic numberings.

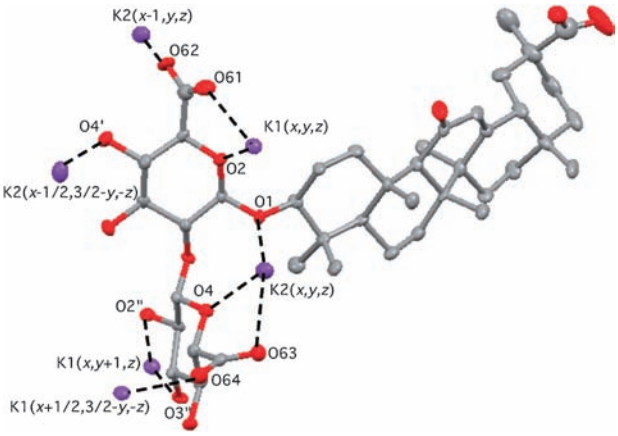

Figure 2. Molecular conformation of **2**. The translation operation of each potassium ion is given in parenthesis. The broken lines show coordination bonds.

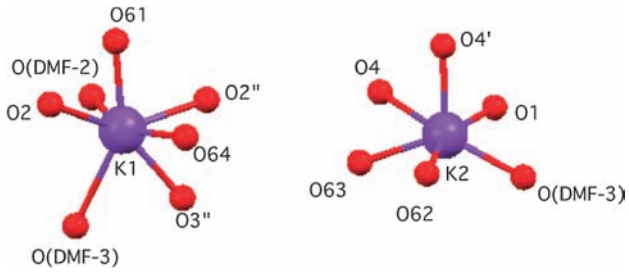

Figure 3. Coordination modes of K1 and K2 atoms. The coordination distances are as follows: K1–O2, 2.849; K1–O61, 2.718; K1–O(DMF-2), 2.734; K1–O64, 2.725; K1–O2″, 2.771; K1–O3″, 2.814; and K1–O(DMF-3), 3.269 Å and K2–O1, 3.096; K2–O4, 3.129; K2–O63, 2.662; K2–O(DMF-3), 2.667; K2–O4′, 2.753; and K2–O62, 2.798 Å.

Table 1. Selected structural data

Bond distance (Å) and angle (°) of carboxyl group					
C30–O30	1.240(9)	C30–O31	1.259(8)	O30–C30–O31	122.7(7)
C6′–O61	1.230(7)	C6′–O62	1.284(7)	O61–C6′–O62	126.9(6)
C6″–O63	1.251(6)	C6″–O64	1.281(7)	O63–C6″–O64	126.5(5)
Torsion angles (°) around diglycoside moiety					
C2–C3–O1–C1′	94.1(5)	C4–C3–O1–C1′	−138.5(4)	H3–C3–O1–C1′ (ϕ1)	−19.4
C3–O1–C1′–C2′	154.2(4)	C3–O1–C1′–O2	−85.7(5)	C3–O1–C1′–H1′ (ϕ2)	38.7
C1′–C2′–O3–C1″	143.9(4)	C3′–C2′–O3–C1″	−97.5(5)	H2′–C2′–O3–C1″ (ϕ3)	24.8
C2′–O3–C1″–C2″	175.6(4)	C2′–O3–C1″–O4	−65.1(5)	C2′–O3–C1″–H1″ (ϕ4)	56.1
Hydrogen bonds (Å) (donor at x, y, z–acceptor at symmetry operation)					
O3′–O62 ($x+1/2$, $-y+3/2$, $-z$)	2.579		O4′–O64 ($x-1$, y, z)		2.594
O2″–O4″ ($x-1/2$, $-y+5/2$, $-z$)	2.678		O2″–O(W1) (x, $y+1$, z)		2.838
O3″–O3′ ($x+1/2$, $-y+5/2$, $-z$)	2.682		O4″–O(W1) ($x+1$, $y+1$, z)		2.718
O(DMF1)–O31 ($-x+1$, $y+1/2$, $-z+1/2$)	2.679		O(W2)–O63 (x, y, z)		2.763

six potassium ions to one molecule (Figure 2), in which two crystallographically independent potassium ions (K1 and K2) and their symmetry-translated four potassium ions coordinate to the oxygen atoms of diglycoside moiety, not aglycon moiety. The coordination modes of K1 and K2 atoms are shown in Figure 3. K1 atom forms seven coordination bonds: O61, O(DMF-3) and O3″ are located at the axial position and four atoms of O2, O64, O2″, and O(DMF-2) in a plane, thus forming a distorted octahedral form. K2 ion forms six coordination bonds with a pyramidal fashion of O4′ at the apex and O1, O4, O63, O62, and O(DMF-3) in a plane.

The present work showed that the trianionic form of **1** has two binding sites for potassium ions. The position of K2 may be more preferable for the coordination with potassium than that of K1, because K2 forms three coordination bonds to an isolated **1**, whereas K1 is limited to two bonds.

In the crystal structure, the aglycon and diglycoside moieties of **2** create discrete hydrophobic and hydrophilic layers, respectively, and these are alternatively expanded perpendicular to the c axis.[9] Potassium ions are located at the diglycoside moiety and stabilize the hydrophilic layers through the coordination bonds and ionic interactions with the hydroxy and carboxyl groups. About two-thirds of the unit cell are sparsely occupied with the aglycon moieties, resulting in fragile crystal packing. DMF and water molecules locate at these sparsely occupied spaces through the hydrogen bonds and stabilize the crystal structure.

References and Notes

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5 $C_{42}H_{60}K_2O_{16}\cdot 3C_3H_7NO\cdot 2H_2O$, orthorhombic, $P2_12_12_1$, $a = 9.799(1)$, $b = 11.186(1)$, $c = 52.228(7)$ Å, $V = 5725.1(22)$ Å^3, $Z = 4$, $F(000) = 2472$, $T = 90$ K, $\theta_{max} = 28.28°$, $D_{calcd} = 1.339$ g cm^{-3}, $D_{measd} = 1.315$ g cm^{-3} μ(Mo Kα) $= 0.243$ mm^{-1} 13543 independent reflections measured, 7436 reflections of $I > 2\sigma(I)$, 691 parameters used for refinement, $R_1 = 0.0858$ (for $I > 2\sigma(I)$), $wR_2 = 0.2207$ (for all data), GOF $= 0.995$. X-ray data were collected with a Bruker SMART APEX CCD diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å) at 90 K. The positions of H atoms, except those of a disordered DMF, were all located on the difference Fourier map and were treated as riding with fixed isotropic displacement parameters ($U_{iso} = 1.2U_{eq}$ for the associated C atoms, or $U_{iso} = 1.5U_{eq}$ for methyl C or O atoms); their atomic positions were not included as variables for the refinements. Crystallographic data reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-729749. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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9 Crystal packings, viewed from a and b axes, are available electronically as Electronic Supporting Information on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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